REMARKS

Reconsideration is requested.

Claims 9, 10, 15-18, 22, 25, 26, 34 and 35 have been canceled, without prejudice. Claim 36 has been added.

Claims 1-14, 18-21 and 23-35 are pending. Upon entry of the present Amendment, claims 1-8, 11-14, 19-21, 23, 24, 27-33 and 36 will be pending.

The Examiner is requested to return an initialed copy of the PTO-1449 Form, filed with an Information Disclosure Statement on December 20, 2006, to the undersigned.

The Examiner is also requested to confirm that the figures filed September 7, 2004, are acceptable or advise the undersigned of any specific objection or rejection of the same.

Claim 1 has been amended by defining the cofactor as an unsaturated C16-C18 fatty acid with a double bond in the cis configuration. As the conformation of C18:1:9 and C:1:11 includes a double bound in the cis confirmation, a fatty acid with a conformation similar hereto is an unsaturated fatty acid with a double bound in the cis conformation (specifications page 3, line 13). The examples and figures describe the testing of several fatty acids and biological activity is observed for C16 and C18 unsaturated fatty acids with a double bound in the cis configuration.

The recitations of subparagraphs (iii) and (iv) of claims 1 and 4 have been deleted, without prejudice.

Claim 2 has been amended by defining the cofactor as an unsaturated C16-C18 fatty acid with 1 to 3 double bonds in the cis configuration with basis in the examples and figures as described above. Claim 5 has been amended to be consistent with the revisions to claim 1. Claims 9 and 10 have been cancelled, without prejudice, as a consequence of the amendments to claim 1. Claims 11 and 12 have been revised to depend from claim 1. Claims 18 and 19 have been amended with basis in the application at, for example, page 4, lines 34-36 and page 1, lines 13-14 specifying the biologically activity associated with the complex. Claims 20-21 and 23-24 have been revised with regard to dependency. Claims 25 and 26 have been cancelled, without prejudice. The recitations of subparagraph (iii) of claim 29 has been deleted, without prejudice. Claims 30-33 are maintained as previously presented. Claims 34-35 have been cancelled, without prejudice, as a consequence of the amendments to claim 29 New claims 36 and 37 have been added with basis, for example, in claims 18 and 19.

The claims have been amended, without prejudice, to advance prosecution.

The claim amendments obviate the claim objections noted on page 2 of the Office Action dated January 25, 2008. Entry of the Amendment and withdrawal of the objections are requested.

The Section 112, second paragraph, rejection of claims 1-14, 18-21 and 23-28 is obviated by the above amendments. Entry of the present Amendment and withdrawal of the rejection are requested. Entry of the present Amendment will at least reduce the issues for appeal by obviating this rejection.

The Section 112, first paragraph "written description", rejection of claims 1-14, 18-21 and 23-35 is obviated by the above amendments. Entry of the present Amendment and withdrawal of the rejection are requested. Specifically, claims 1 and 2 have been amended to delete the alleged "new matter", without prejudice and to advance prosecution. Moreover, the objected-to recitation relating to 100 amino acids in length has been deleted, without prejudice, to advance prosecution.

Claims 19 and 36 further include a description of functional aspects of the disclosed invention. The applicants submit that a representative number of species of alpha-lactalbumin variants are disclosed in the specification and that one of ordinary skill in the art will appreciate that the applicants were in possession of the claimed invention at the time the application was filed.

Claims 6-8 relate to variants in which the calcium binding site has been modified, which are exemplified by SEQ ID NO: 3 and SEQ ID NO: 4 (subject of claim 8), which is a representative number of such variants.

Claims 20-21 and 23-24 are relate to variants which include conservative amino acid substitutions, which will be recognized by one of ordinary skill in the art.

In conclusion at the time of filing the application the applicant had possession of several alpha-lactalbumin sequences and mutants thereof which displayed biological activity in complex with a cofactor as defined in the application and claims. Furthermore, the ordinarily skilled person is capable of preparing and testing further mutants or variant as discussed in the "Revised Interim Written Description Guidelines Training Materials" (http://www.uspto.gov/web/offices/pac/writtendesc.pdf) example 14.

Therefore the written description requirement has been fulfilled for alpha-lactalbumin and alpha-lactalbumin variants as defined in the claims.

Withdrawal of the Section 112, first paragraph "written description", rejection is requested.

The Section 102 rejection of claims 1-3, 5, 13, 14, 18, 19, 20, 23 and 26-30 over Svensson ("Conversion of α-lactalbumin to α-lactalbumin a protein inducing apoptosis", PNAS (April 11, 2000), Vol. 97, No. 8, pp 4221-4226), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner is requested to appreciate that claim 1 and claims dependent therefrom, as rejected and as amended above, define compositions and complexes which do not include C18:1:9 cis (oleic acid).

Svensson describes an active complex which

> "consist[s] of partially unfolded [human] α-lactalbumin that has integrated a cofactor, which stabilizes the conformation. The cofactor has been identified as a **specific** fatty acid." See page 4221, right column, lines 3-6 of Svensson (emphasis added).

Svensson isolated casein from human milk and separated fatty acids therefrom. See Materials and Methods "Identification of the Cofactor on the Casein-Conditioned Column Matrix" . Svensson teaches conditioning an ion-exchange matrix with fatty acids

> "palmitic acid (16:0), steric acid (18:0), myristic acid (14:0), or **oleic acid (18:1)**" See Materials and Methods "Fatty Acid Conditioning of the Ion-Exchange Matrix" (emphasis added).

Svensson describes that the

> "cofactor was identified by chemical extraction of the casein-conditioned matrix under conditions suitable for proteins or lipids. …Individual lipid species were identified by GC/MS as C18:1, C16:0, and C14:0 fatty acids (data not shown).
>
> New column matricies then were conditioned with each of the fatty acids or with C18:0 and exposed to whey-derived or recombinant α-lactalbumin in the native or apo states…. α-Lactalbumin from human milk whey and recombinant protein was shown to convert to the active complex only on the C18:1 fatty acid-preconditioned column and only when applied in the apo form…. The C18:1-converted apo α-lactalbumin from human milk whey was named HAMLET and the converted recombinant apo α-lactalbumin was named recombinant HAMLET. …
>
> <u>These results identified the C18:1 fatty acid as the responsible cofactor required to convert α-lactalbumin to HAMLET</u>." <u>See</u> Results "Identification of the Cofactor" (emphasis added).

The <u>only</u> C18:1 fatty acid described in Svensson is "oleic acid". Moreover, the only fatty acid described by Svensson which contains a double bond is oleic acid (C18:1 fatty acid), which is described by Svensson as being critical ("obligatory"; <u>see</u> page 4226, left column of Svensson) to make human α-lactalbumin lethal to tumor cells (i.e., critical to producing HAMLET). <u>See</u> also page 4226, left column of Svensson ("First, we used α-lactalbumin from human milk whey rather than from casein, showed that is was inactive, and then activated it by partial unfolding and exposure to **<u>oleic acid</u>**." (emphasis added)).

While "C18:1 fatty acid could be represented by C18:1:11 or C18:1:9", as asserted by the Examiner (<u>see</u> page 8 of the Office Action dated January 25, 2008), the

relevance of the statement is unclear in the context of the specific teachings of Svensson. Specifically, Svensson requires oleic acid (i.e., C18:1:9) as a critical component of the HAMLET complex. The present claims 1, and claims dependent therefrom, do not include this critical component of Svensson. Svensson fails to teach each and every aspect of the claimed invention defined by claim 1 and claims dependent therefrom. Claim 1 and the claims dependent therefrom are not anticipated by Svensson and withdrawal of the Section 102 rejection of the same based on Svensson is requested.

The complexes of claim 29, and claims dependent therefrom, which include oleic acid as a cofactor, do not include human α-lactalbumin, as required by Svensson. Claim 29, and claims dependent therefrom, therefore are submitted to also be patentable over Svensson.

Withdrawal of the Section 102 rejection of claims based on Svensson is requested.

The Section 102 rejection of claims 1-5, 13, 14, 18, 19 and 26-30 over Hakansson (Molecular Biology, 2000, 35(3), pages 589-600), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following distinguishing comments.

The disclosure of Hakansson resembles the disclosure by Svensson by disclosing oleic acid as the C18:1 fatty acid cofactor. See for example, Experimental Procedures "Conversion of α-lactalbumin to the active form", page 598, right column, second full paragraph of Hakansson.

The claims are submitted to be patentable over Hakansson and withdrawal of the Section 102 rejection based on the same is requested.

The Section 103 rejection of claims, 1, 6-8, 29, 31 and 32 over Svensson in view of Permyakov (Protein Engineering, Vol. 14, No. 10, pp 785-789, 2001), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following further comments.

The deficiencies of Svensson noted above are not cured by Permyakov. Svensson teaches away from the presently claimed invention in that components not found in the presently claimed invention are critical to the complexes of Svensson. Moreover, Permyakov does not further address the identity of the cofactor of the claims.

The cited art fails to teach or suggest a biologically active complex according to the claimed invention which comprises a mutant. The cited art fails to suggest any reasonable expectation of success of obtaining a biologically active complex by substituting wild type alpha-lactalbumin with a calcium binding mutant of alpha-lactalbumin, as claimed.

Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. Entry of the Amendment is requested.

Respectfully submitted,

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